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L-Proline-functionalized magnetic nanocomposite: a green magnetic nanocatalyst for efficient synthesis of 3-amino imidazo[1,2-*a*]pyridines

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Abstract

In this work, an efficient method for the immobilization of L-proline on magnetic nanoparticles was offered and evaluated as a recoverable magnetic organocatalyst for synthesis of 3-aminoimmidazo[1,2-*a*]pyridine from 2-aminopyridine, aromatic aldehyde and trimethylsilyl cyanide (TMSCN). This magnetic organocatalyst proved to be effective and provided the products in high to excellent yield at room temperature. Moreover, the catalyst could be easily recovered by facile separation by magnetic forces and recycled for five times without significant loss of its catalytic activity. The benefits of this study are simplicity, nontoxicity, low cost, simple workup, and an environmentally benign nature.

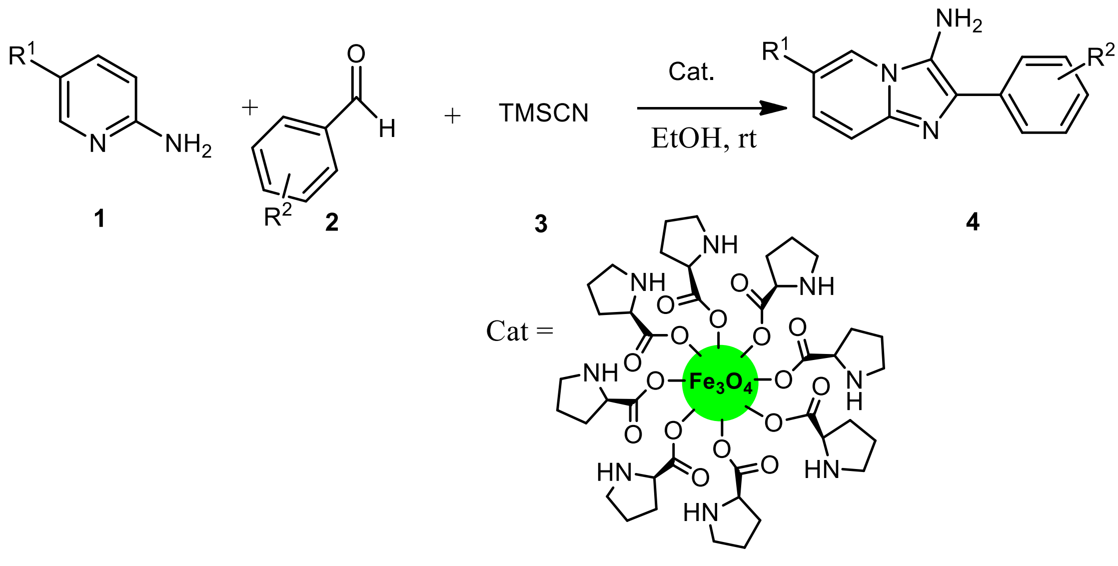
Keywords: Green chemistry, Magnetic nanocatalysts, Organocatalysis, Proline, Imidazo[1,2-*a*]pyridines.

1. Introduction

Nowadays, magnetic nanocatalysts have attracted much attention as beneficial strategy in green chemistry[1,3]. They combine the advantages of both homogeneous and heterogeneous catalysts like high dispersion, high reactivity and easy separation because of their nanoscale size and magnetic properties. Organocatalysis has received considerable attention in organic synthesis. Among all organocatalysts, proline has shown considerable catalytic efficiency in different organic synthesis due to easily accessible and available in both enantiomeric forms[4]. Recently, much interest has been paid to the immobilization of organocatalyst onto magnetic nanoparticles for catalytic application in organic reactions[5].

Imidazo[1,2-*a*]pyridines are an important class of nitrogen based heterocyclic compounds, which have been widely used in pharmaceutical industry due to their interesting biological activities[6,7]. So far, several methods have been reported for the synthesis of this important frameworks[8-10].

In continuation of our research[11-18], herein, an efficient and selective synthesis of 3-amino imidazo[1,2-*a*]pyridine derivatives were carried out using aromatic aldehydes, 2-aminopyridines and trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of L-proline-functionalized magnetic nanocatalyst (Fe_3O_4@L-proline) in ethanol at room temperature in high yields (Scheme 1). The solid nanocatalyst can be recovered easily and reused without any significant loss of the catalytic activity.



Scheme 1. Synthesis of 3-aminoimidazo[1,2-*a*]pyridines in the presence of Fe_3O_4@L-proline.

2. Experimental

2.1. General

All chemicals and reagents were purchased from Merck, Fluka and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer by the method of KBr pellet. All the products were known compounds and were identified by comparison of their spectroscopic and analytical data with those authentic samples.

2.2. Preparation of Fe_3O_4@L-proline magnetic nanoparticles

Fe_3O_4@L-proline magnetic nanoparticles was prepared via in situ coprecipitation method. In a typical procedure, $FeCl_3 \cdot 6H_2O$ (0.54 g) and $FeCl_2 \cdot 4H_2O$ (0.2 g) at a molar ratio of 2: 1 were dissolved in 100 ml of deionized water and and vigorously stirred at 40°C for 15 min with a mechanical stirrer. After that, 0.3 g of L-proline and NH_4OH solution (25 wt%) were added to the mixture until the pH was reached to 11 to produce black precipitate. Then, this mixture was refluxed at 100°C for 6 h, with vigorous stirring. Finally, the black precipitate was collected using an external magnet and washed several times with ethanol and distilled water and dried at 80 °C in an oven.

2.3. General procedure for the synthesis of 3-aminoimidazo [1, 2-a] pyridine ***(4a-l)***

A mixture of an aromatic aldehyde (1.0 mmol), 2-amino pyridine (1.0 mmol), TMSCN (1.2 mmol) and Fe_3O_4@L-proline magnetic nanoparticles (0.01g) in EtOH (4 mL) was stirred at room temperature. The completion of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the catalyst was separated easily by an external magnet. The pure products were obtained from the reaction mixture by recrystallization from ethylacetat and no more purification was required.

3. Results and discussion

In this study, we have synthesized an efficient magnetic organocatalyst Fe_3O_4@L-proline. The FT-IR spectrum of Fe_3O_4@L-proline can verify the preparation of the expected product. The bending vibration band at 588 cm^{-1} is indicated Fe–O vibration. In addition, two bands appearing at 1627 and 1415 cm^{-1}, are ascribed to asymmetric νs (COO^-) and symmetric νs (COO^-) stretching of carboxyl group[19]. Furthermore, the asymmetric stretching vibrations of O–H and N–H groups observed at around 3384-3448 cm^{-1}. These results indicate that L-proline was successfully composed onto the surfaces of Fe_3O_4 nanoparticles.

In order to examine the generality of this nanocatalyst for the construction of 3-amino immidazo[1,2-*a*]pyridine derivatives, a series of electron rich and deficient aromatic aldehydes, 2-aminopyridine and trimethylsilylcyanides, were employed and a variety of products were synthesized under the optimized conditions the results are summarized in Table 1. It was indicated that both electron deficient and electron rich aromatic aldehydes a wide range of immidazo[1,2-*a*]pyridine derivatives in good to excellent yields.

Table 1. Synthesis of 3-aminoimidazo[1,2-a] pyridines in the presence of Fe_3O_4@L-proline magnetic nanoparticles.

Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)	Mp (°C)	
						Observed	Literature
1	CH_3	H	**4a**	1	75	245-246	248-250 [20]
2	CH_3	4-Cl	**4b**	1	89	235-237	230 [20]
3	CH_3	4-CH_3	**4c**	1	82	244-245	250 [20]
4	H	4-OCH_3	**4d**	1	80	217-218	212-214 [20]
5	H	4-NO_2	**4e**	1	83	210-211	215-218 [20]

[a] Isolated yield.

4. Conclusions

In summary, we have introduced a green, magnetically recyclable, environmentally-friendly and efficient composite nanocatalyst (Fe_3O_4@L-proline) for the selective synthesis of 3-amino imidazo[1,2-*a*]pyridine derivatives. The efficient and selective syntheses of 3-amino imidazo[1,2-*a*]pyridine derivatives were carried out using different aromatic aldehydes, 2-

aminopyridines and trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of L-proline-functionalized magnetic nanocatalyst (Fe_3O_4@L-proline) in ethanol at room temperature in high yields. Finally, the catalyst can be easily separated by an external magnet and recycled for several times without any appreciable loss of activity.

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References

1. A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.*, **2008**, 47, 4638-4660.
2. B. List, J.W. Yang, *Science*, **2006**, 313, 1584-1586.
3. S. Mayer, B. List, *Angew. Chem. Int. Ed.*, **2006**, 45, 4193-4195.
4. B. List, *Tetrahedron*, **2002**, 58, 5573–5590.
5. K. Vishal, B.D. Fahlman, B.S. Sasidhar, S.A. Patil, S.A. Patil, *Catal. Lett.*, **2017**, 147, 900-918.
6. T.H. Al-Tel, M.H. Semreen, R.A. Al-Qawasmeh, M.F. Schmidt, R. El-Awadi, M. Ardah, R. Zaarour, S.N. Rao, O. El-Agnaf, *J. Med. Chem.*, **2011**, 54, 8373-8385.
7. N. Dahan-Farkas, C. Langley, A.L. Rousseau, D.B. Yadav, H. Davids, C. B. de Koning, *Eur. J. Med. Chem.*, **2011**, 46, 4573-4583.
8. S. Santra, A.K. Bagdi, A. Majee, A. Hajra, *Adv. Synth. Catal.*, **2013**, 355, 1065-1070.
9. C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han, A. Lei, *Chem. Commun.*, **2012**, 48, 11073-11075.

10. B. Maiti, K. Chanda, M. Selvaraju, C.C. Tseng, C.M. Sun, *ACS. Comb. Sci*., **2013**, 15, 291-297.

11. A. Maleki, *Tetrahedron*, **2012**, 68, 7827-7829.

12. A. Maleki, *Helv. Chim. Acta*, **2014**, 97, 587-593.

13. A. Maleki, N. Ghamari and M. Kamalzare, *RSC Adv.*, **2014**, 4, 9416-9423.

14. A. Maleki, M. Kamalzare, *Catal.Commun*., **2014**, 53, 67-71.

15. A. Maleki, R. Rahimi, S. Maleki, N. Hamidi, *RSC Adv*., **2014**, 4, 29765-29671.

16. A. Maleki, R.Firouzi Haji, M. Ghassemi, H. Ghafuri, *J. Chem. Sci.*, **2017**, 129, 457–462.

17. A. Maleki, E. Akhlaghi, R. Paydar. *Appl. Organomet. Chem*., **2016**, 30, 382-386.

18. A. Maleki, P. Zand, Z. Mohseni. *RSC Adv.*, **2016**, 6, 110928-110934.

19. J. Safaei-Ghomi, S. Zahedi, *Appl. Organomet. Chem*., **2015**, 29, 566-571.

20. A. Shaabani, A. Maleki, *Monatsh. Chem.*, **2014**, 138, 51-56.